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(54) **Pharmaceutical composition containing choline ester salts for enhancing gastrointestinal tract absorption.**

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US-A- 4 171 353

CHEMICAL ABSTRACTS, vol. 70, 1969, page 202, abstract no. 113707z, Columbus, Ohio, US; K.I. KHADZHAI et al.: "Effect of flavonoid compounds on some functions of the gastrointestinal tract", & FENOL'NYE SOEDIN. IKH BIOL. FUNKTS., MATER. VSES. SIMP., 1ST 1966 (PUB. 1968), 365-71

(73) Proprietor: **MERCK & CO. INC.**
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065-0900(US)

(72) Inventor: **Alexander, Jose**
2909 Westdale Court
Lawrence Kansas 66044(US)
Inventor: **Fix, Joseph A.**
824 Mississippi
Lawrence Kansas 66044(US)

(74) Representative: **Ahner, Francis et al**
CABINET REGIMBEAU, 26, avenue Kléber
F-75116 Paris(FR)

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CHEMICAL ABSTRACTS, vol. 56, 1962, c l-umn 9358c-g, Columbus, Ohio, US; I. KENICHI et al.: "Effects of streptomycin on the action of muscle relaxants", & MED. J. SHINSHU UNIV. 3, 299-310(1958)

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CHEMICAL ABSTRACTS, vol. 76, 1972, page 96, abstract no. 61261b, Columbus, Ohio, US; I.P. KOMKOV et al.: "Surface-active quaternary ammonium salts of o-acylcholines", & IZV. VYSSH. UCHEB. ZAVED., KHIM. KHIM. TEKHNOL. 1971, 14(9), 1369-73

Description

BACK GROUND OF THE INVENTION

The invention relates to novel compositions and methods for enhancing absorption of drugs from the gastrointestinal tract by incorporating therein a choline ester salt absorption enhancing agent.

DESCRIPTION OF THE PRIOR ART

Though the gastrointestinal tract is the preferred route for drug delivery, all drugs are not well absorbed from this site. In many cases, this may be due to the polar nature or hydrophilic character of the drugs. Since they are precluded from rapid absorption, such drugs are subject to long residency time in the gastrointestinal environment where both acidic and enzymatic degradation contribute to their poor bioavailability. It is, therefore, clear that any factor which enhances the rate of absorption will demonstrate improved clinical efficacy. In recent years, considerable effort has been directed toward identifying agents which increase gastrointestinal absorption of poorly absorbed drugs. For example, surface active agents (George, Sutter, Finegold, J. Infect. Dis. 136, 822 (1977), chelating agents (Cassidy, Tidball, J. Cell Biol. 32, 672 (1967), salicylates (Higuchi, et al., U.S. Patent 4,462,991 (1984)), antiinflammatory agents (Yaginuma et al., Chem. Pharm. Bull. 29, 1974 (1981) and phenothiazines (Alexander and Fix, U.S. Patent 4,425,337 (1984) have been shown to increase gastrointestinal permeability of a variety of drugs.

The state the of art is also illustrated by Chemical Abstracts 70 (1969), page 202, n° 1137072, which is directed to the "Effect of flavonoid compounds on some function of the gastrointestinal tract". The reference states that flavonoids depress the tonus of smooth muscles of rabbits, cats, rats and guinea pigs. Said reference further states that tonus which was previously increased by administration of $BaCl_2$, acetylcholine or histamine, was depressed by flavonoids.

The present use of choline esters to promote gastrointestinal absorption affords several advantages over the prior art's absorption promoting compounds. The choline esters, especially those with medium and long chain fatty acid components, are more potent than the presently used absorption promoting agents. As an example, in aqueous solutions, the choline esters are effective absorption promoting agents at levels as low as 0.05%. By contrast, the effective dose of other known absorption promoters is significantly higher: sodium salicylate - 1%, surfactants - 1%, chelating agents - 2%. This difference in potency affords opportunities for reducing the required size of the dosage form and potentially minimizing side effects. The choline esters cause reversible changes in gastrointestinal permeability to the target drug, indicating that a permanent change has not occurred. Other promoting agents, such as the surfactants, cause a relatively permanent change in gastrointestinal permeability, which is only overcome by turnover of the mucosal cells, a process which may require days for completion. By contrast, removal of choline esters from the gastrointestinal tract results in reversion to normal permeability properties in less than 2 hours. This provides a significant advantage in that a rapid and reversible increase in drug absorption does not allow prolonged intervals during which potentially toxic or otherwise harmful agents might also be absorbed. Another potential advantage of the choline esters is that, unlike chelating agent such as EDTA, the choline esters may not necessarily sequester divalent cations (Mg^{++} or Ca^{++}) which are necessary for the normal functioning of cells. In other words, there is no tissue damage at concentrations of choline esters which significantly increase drug absorption. In contrast to this, studies have indicated that surfactant activity, as with sodium lauryl sulfate, is generally associated with some degree of cellular damage. This lack of tissue damage affords a significant advantage to the use of choline esters in promoting gastrointestinal drug absorption. An added advantage is that they can be metabolized through normal pathways in the body. Thus, on enzymatic hydrolysis the choline esters produce choline and a fatty acid, both of which are normal endogenous components and nutritive agents. This eliminates a potential problem of introducing substances which are not normally present in the biochemical pathways of the body (e.g. salicylates and, EDTA)

SUMMARY OF THE INVENTION

It has been found that when poorly absorbed drugs are administered orally or rectally, the bioavailability of said drugs is increased by incorporating therein a choline ester salt absorption enhancing agent.

Accordingly, it is an object of this invention to enhance the bioavailability of poorly absorbed drugs administered orally or rectally by administering therewith a choline ester absorption enhancing agent.

A further object of the invention is to provide a new dosage form utilizing a class of choline esters which

when administered orally or rectally with a therapeutic agent will provide an increased blood level of said therapeutic agent.

Another object of the invention is to provide a choline ester absorption promoter of gastrointestinal and rectal drug absorption at concentrations which do not alter the normal morphology of the mucosal cells.

Still another object of the invention is to provide a choline ester series of absorption enhancing agents that are endogenous and can be metabolized through normal pathways available in the body.

Other objects, features and advantages of the invention will be apparent to those skilled in the art from the detailed description of the invention which follows.

All of the foregoing objects are readily attained by providing a composition and method wherein oral and rectal absorption of poorly absorbed drugs is enhanced. The method comprises the steps of preparing a dosage form suitable for oral or rectal delivery, and a dosage form comprising an effective unit dosage amount of the poorly absorbed drug, a choline ester salt absorption agent, the agent being present in said dosage form in an amount sufficient to be effective in enhancing the rate of the oral and rectal absorption of the therapeutic agent, and pharmaceutically acceptable excipients.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a pharmaceutical composition for enhancing gastrointestinal tract absorption of an orally or rectally administered drug comprising a therapeutically effective dosage amount of a drug which is a β-lactam antibiotic selected from cefoxitin, ampicillin, cefamandole, cefazoline, cefotaxime, cefaclor, cephalexine, ceftriaxone, ceftizoxime, sarmoxacillin, N-formamidinyl-thienamycin, cefadroxil, penicillin G. and penicillin V.; an aminoglycoside selected from gentamycin, neomycin, clindamycin, astromicin, betamicin and josamycin; an antiviral agent selected from cytarabine, acyclovir, trifluridine, and vidarabine; an amino acid selected from methyldopa, levodopa and carbidopa; a smooth muscle relaxant selected from aminophylline, zanthinol niacinate and glucophylline; a polypeptide selected from gastrin, somatostatin, insulin and cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe) acetate; an anti-inflammatory agent selected from indomethacin and sulindac; or a diuretic selected from hydrochlorothiazide, amiloride and chlorothiazide and a choline ester absorption enhancing agent of the formula :

$$[CH_3)_3N^{\bullet} + CH_2CH_2OR]X^{-}$$

wherein R is saturated acyl (C_2-C_{20}), acyl (C_2-C_{20}) with 1 to 6 double bonds, hydroxyacyl (C_2-C_{20}) with 1 to 3 hydroxy groups, ketoacyl (C_4-C_{20}), unsaturated hydroxyacyl (C_5-C_{20}), carbalkoxyacyl (C_5-C_{20}) or carboxyacyl (C_4-C_{20}) and X is a pharmaceutically acceptable counterion, such as chloride, sulfate, nitrate, perchlorate, bromide, iodide, phosphate, acetate, benzoate, tartrate, citrate, propionate, gluconate, lactate, maleate, fumarate, bezylate, camsylate, esylate, gluceptate, mesylate or napsylate.

The preferred oral and rectal absorption enhancing agents of the above formula are:

1. hexanoylcholine
2. lauroylcholine
3. octanoylcholine
4. myristoylcholine
5. palmitoylcholine
6. stearoylcholine
7. 2-hexenoylcholine
8. 9-decenoylcholine
9. 9-hexadecenoylcholine
10. α-linoleoylcholine
11. 2-hydroxylauroylcholine
12. 6-ketodecanoylcholine
13. ω-ethoxycarbonyloctanoylcholine
14. 2-hydroxypalmitoylcholine

The most preferred absorption enhancing agents useful in our method and dosage forms are:

1. hexanoylcholine
2. octanoylcholin
3. decanoylcholine
4. lauroylcholine
5. myristoylcholin
6. palmitoylcholine

7. stearoylcholine

The choline ester salt absorption enhancing agents employed in the practice of this invention are known compounds which are commercially available and processes for their preparation are disclosed throughout the art.

Various active agents provide beneficial effects when administered to patients. Such agents which can be made more useful by enhancing their absorption in accordance with this invention, are exemplified by, the following classes of drugs:

1) β-lactam antibiotics such as cefoxitin, N-formamidinyltheinamycin, ampicillin, azlocillin, bacampicillin, carbenicillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazoline, cefonicid, cefaperazone, ceforanide, cefotaxime, cefotiam, cefroxadine, cefsulodin, ceftazidime, ceftriaxone, ceftizoxime, cephalexin, cephaloglycin, cephaloridine, cephradine, cyclacillin, cloxacillin, dicloxacillin, floxacillin, hetacillin, methicillin, nafcillin, oxacillin, sarmoxacillin, sarpicillin, talampicillin, ticaricillin, penicillin G., penicillin V., pivampicillin, piperacillin or pirbenicillin.

2) Aminoglycoside antibiotics such as gentamycin, amikacin, astromicin, betamicin, butikacin, butirosin, clindamycin, josamycin, kanamycin, neomycin, netilmicin or tobramycin.

3) Antiviral agents such as ara C (cytarabine), acyclovir, floxuridine, ribavirin, vidarabine, idoxuridine or trifluridine.

4) Amino acids such as methyldopa, carbidopa, levodopa, fludalanine or γ-aminobutyric acid.

5) Smooth muscle relaxants such as theophylline, aminophylline, diphylline, oxtriphylline, ambuphylline, fenethylline, guathylline, pentoxyfylline, xanthinol niacinate or glucophylline.

6) Polypeptides such as cyclo(N-Ala-Tyr-D-Trp-Lys-Val-Phe)acetate, somatostatin, inslulin, gastrin, caerulein or cholecystokinin.

7) Anti-inflammatory agents such as indomethacin, sulindac or ibuprofen.

8) Diruetics such as aldactone, hydrochlorothiazide, amiloride, chlorothiazide or furosemide.

The enhancement of drug absorption in accordance with this invention is not by any means limited to the above drugs, but are in general applicable to other classes of drugs such as analgesics, anabolics, androgens, anorexics, adrenergics, antiadrenergics, antiallergics, antibacterials, anticholinergics, antidepressants, antidiabetics, antifungal agents, antihypertensives, antineoplastics, antipsychotics, sedatives, cardiovascular agents, antiulcer agents, anticoagulants, anthelmintics, radio-opaques or radionuclide diagnostic agents.

The amount of poorly absorbed drug varies over a wide range, however the therapeutically effective unit dosage amount of the selected poorly absorbed drug depends on that amount known in the art to obtain the desired results.

Generally, the amount of adjuvant employed in the practice of the invention ranges from 0.05-500 mg in each unit dose. The percentage of adjuvant in the total combination of drug plus adjuvant is 0.05-50% with a preferred ratio of adjuvant in the total combination of adjuvant plus drug being 0.5-25%. The remaining percent being the drug and optionally other excipients.

For oral administration, the formulations may be prepared as liquids, suspensions, capsules, tablets, coated tablets, and other standard procedures known in the art. The preferred formulation is a compressed tablet composed of a minimum of 1 mg choline ester with the pharmacologically required dose of drug and sufficient excipients to formulate an acceptable composition. For rectal application, the formulations may be prepared as microenemas, suppositories, rectal tablets, and other standard procedures known in the art. The preferred formulation is a solid suppository composed of a minimum of 1 mg choline ester with the pharmacologically required dose of drug and sufficient suppository base to formulate an acceptable composition. The methods and choice of excipients and suppository bases are well known to those skilled in the art and the composition of said formulations is not limited to compressed tablets or solid suppositories by this invention.

The following examples illustrate preparation of various compositions of the invention.

EXAMPLE 1

Effect of lauroyl choline chloride and palmitoyl choline iodide on the rectal absorption of drug entities.

Experiments were performed with rats wherein each animal received an aqueous microenema applied to the rectal cavity. The microenemas contained target drug entity (amount shown in table) in the presence or absence of 5 mg lauroylcholine chloride or palmitoylcholine iodide. Blood levels were monitored and the amount of drug absorbed calculated against intravenous administration and expressed as percent bioavailability.

Target Drug	Dose	Drug Class	Percent Bioavailability (mean ± SD) with		
			Control	Lauroyl choline chloride	Palmitoyl choline iodide
Sodium cefoxitin	2.5 mg	β-lactam antibiotic	2 ± 1.1	100 ± 13.2	56 ± 4.1
Gentamicin sulfate	2.5 mg	aminoglycoside antibiotic	4 ± 1.2	132 ± 43.3	---
Cytarabine	2.5 mg	anti-viral anti-neoplastic	0.5 ± 0.1	71 ± 8.5	51 ± 8
*Theophylline	2.5 mg	smooth muscle relaxant	75 ± 3.3	66 ± 4.9	36 ± 3.4
**	0.1 mg	polypeptide	7 ± 3.5	132 ± 43.3	27 ± 9.8
Methyldopa	2.5 mg	cardiovascular anti-hypertensive	6 ± 0.3	90 ± 15.5	45 ± 12.8

** cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe)acetate -*(comparison example). The drug is absorbed well by itself.

EXAMPLE 2

Effect of various choline esters on rectal absorption of sodium cefoxitin, a β-lactam antibiotic, and cyclo(N-Ala-Tyr-D-Trp-Lys-Val-Phe)acetate, a polypeptide.

Each animal received an aqueous microenema. pH 6, containing 2.5 mg sodium cefoxitin or 0.1 mg cyclo(N-Ala-Tyr-D-Trp-Lys-Val-Phe)-acetate and 5.0 mg various choline esters of the general formula of this invention. Blood samples were collected and sodium cefoxitin or cyclo(N-Ala-Try-D-Trp-Lys-Val-Phe)acetate assayed. The amount of drug absorbed is expressed as percent bioavailability versus intravenous administration

Choline Ester Salt	Percent Bioavailability (mean ± SD)	
	Sodium Cefoxitin*	**
None	2 ± 1.1	7 ± 3.5
Lauroylcholine-Cl	100 ± 13.2	132 ± 43.3
Myristoylcholine-Cl	32 ± 4.6	100 ± 45.0
Palmitoylcholine-I	56 ± 4.1	27 ± 9.8
Stearoylcholine-I	27 ± 6.8	26 ± 5.1

* β-lactam antibiotic
** Cyclo(N-Ala-Try-D-Trp-Lys-Val-Phe)acetate

EXAMPLE 3

Importance of choline palimitoyl ester linkage in absorption promoting effects on rectal sodium cefoxitin absorption.

Each animal received an aqueous microenema, pH 6, containing 2.5 mg sodium cefoxitin in the presence or absence of 5.0 mg palmitic acid, choline or palmitoylcholine iodide. Blood was collected and sodium cefoxitin measured. Absorption of sodium cefoxitin is expressed as percent bioavailability versus intravenous administration.

Compound	Sodium Cefoxitin Percent Bioavailability (mean ± SD)
None	2 ± 1.1
Palmitic acid	1 ± 0.8
Choline	1 ± 0.6
Palmitoylcholine-I	56 ± 4.1

EXAMPLE 4

Reversibility of absorption promoting effect of choline esters.

Two separate experiments with two choline esters demonstrate that these esters cause no permanent change in rectal mucosal tissue at concentrations which effectively increase drug absorption. In these experiments animals are treated with 5.0 mg of lauroylcholine-Cl or palmitoylcholine-I alone and then tested for sodium cefoxitin absorption either immediately or after 1 hour or 2 hours of recovery. Sodium cefoxitin absorption is expressed as percent bioavailability and indicates the reversibility of the absorption promoting effect upon removal of the choline ester.

Interval Between Administrations (min)	Sodium Cefoxitin Percent Bioavailability	
	with Lauroyl choline Chloride	with Palmitoylcholine iodide
0	100 ± 13.2	56 ± 4.1
60	24 ± 2.8	1 ± 0.5
120	5 ± 6.2	10 ± 1.7

EXAMPLE 5

Effect of choline esters on small intestinal absorption of polypeptides.

Experiments were performed with rats wherein each animal received an aqueous solution applied to the duodenal region. The solutions contained target drug entity 0.1 mg [cyclo(N-Ala-Try-D-Trp-Lys-Val-Phe)-acetate] in the presence or absence of 5 mg of choline esters. Blood levels were monitored and the amount of polypeptide absorbed calculated against intravenous administration and expressed as percent bioavailability.

Adjuvant	Percent Bioavialability (mean ± SD) of **
None	1
Lauroylcholine chloride	8.6 ± 1.4
Palmitoylcholine chloride	6 ± 2

** Cyclo(N-Ala-Try-D-Trp-Lys-Val-Phe)acetate

EXAMPLE 6

Effect of choline esters on small intestinal absorption of cofoxitin.

Experiments were performed as in Example 5. The solutions contained 10 mg/kg of cefoxitin and 20 mg/kg of absorption promoters. Blood levels of cefoxitin were monitored and the bioavailability of cefoxitin absorbed was calculated against intravenous administration.

Adjuvant	Percent Bioavialability (mean ± SD) of cefoxitin
None	2 ± 1.1
Myristoylcholine chloride	32 ± 4.6
Stearoylcholin iodide	20.3 ± 5.9

Claims

1. A pharmaceutical composition for enhancing gastrointestinal tract absorption of an orally or rectally

administered drug comprising a therapeutically effective dosage amount of a drug which is a β-lactam antibiotic selected from cefoxitin, ampicillin, cefamandole, cefazoline, cefotaxime, cefaclor, cephalexine, ceftriaxone, ceftizoxime, sarmoxacillin, N-formamidinyl-thienamycin, cefadroxil, penicillin G. and penicillin V.; an aminoglycoside selected from gentamycin, neomycin, clindamycin, astromycin, betamicin and josamycin; an antiviral agent selected from cytarabine, acyclovir, trifluridine, and vidarabine; an amino acid selected from methyldopa, levodopa and carbidopa; a smooth muscle relaxant selected from aminophylline, zanthinol niacinate and glucophylline; a polypeptide selected from gastrin, somatostatin, insulin and cyclo(N-Me-Ala-Try-D-Trp-Lys-Val-Phe)acetate; an anti-inflammatory agent selected from indomethacin and sulindac; or a diuretic selected from hydrochlorothiazide, amiloride and chlorothiazide, and a choline ester absorption enhancing agent of the formula :

$$[(CH_3)_3N^+CH_2CH_2OR]X^-$$

wherein R is saturated acyl (C_2-C_{20}), acyl (C_2-C_{20}) with 1 to 6 double bonds, hydroxyacyl (C_2-C_{20}) with 1 to 3 hydroxy groups, ketoacyl (C_4-C_{20}), unsaturated hydroxyacyl (C_5-C_{20}), carbalkoxyacyl (C_5-C_{20}) or carboxyacyl (C_4-C_{20}) and X is a pharmaceutically acceptable counterion.

2. A pharmaceutical composition according to claim 1, characterized in that said absorption enhancing agent is selected from hexanoylcholine, octanoylchloline, decanoylcholine, lauroylcholine, myristoylcholine, palmitoylcholine, stearoylcholine, 2-hexenoylcholine, 9-decenoylcholine, 9-hexadecenoylcholine, α-linoleoylcholine, 2-hydroxylauroylcholine, 2-hydroxymyristoylcholine, 6-ketodecanoylcholine, 12-hydroxy-12-octadecenoylcholine, ω-ethoxycarbonyloctanoylcholine and 2-hydroxypalmitoylcholine.

3. The composition of claim 2 wherein said β-lactam antibiotic is cefoxitin, said aminoglyciside is gentamycin, said antiviral agent is cytarabine, said amino acid is methyldopa, said polypeptide is cyclo-(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe)acetate, said anti-inflammatory agent is indomethacin and said diuretic is hydrochlorothiazide and said absorption enhancing agent is palmitoylcholine, lauroylcholine, myristoylcholine, stearoylcholine or its salt.

4. The composition of claim 3, wherein said absorption enhancing agent is lauroylcholine chloride.

5. The composition of claim 3, wherein said absorption agent is palmitoylcholine iodide.

6. The composition of claim 1, further comprising pharmaceutically acceptable excipients.

Revendications

1. Une composition pharmaceutique pour augmenter l'absorption des voies gastrointestinales d'un médicament administré par voie orale ou rectale comprenant une dose thérapeutiquement efficace d'un médicament qui est une antibiotique β-lactamine choisi parmi la céfoxitine, l'ampicilline, la céfamandole, la céfazoline, la céfotaxime, le céfaclor, la céphalexine, la ceftriaxone, la ceftizoxime, la sarmoxacilline, la N-formamidinyle-thiènamycine, le céfadroxil, la pénicilline G et la pénicilline Y ; un aminoglycoside choisi parmi la gentamycine, la néomycine, la clindamycine, l'astromycine, la bétamycine et la josamycine ; un agent antiviral choisi parmi la cytarabine, l'acyclovir, la trifluridine, et la vidarabine ; un acide aminé choisi parmi la méthyledopa, la levodopa et la carbidopa ; un relaxateur des muscles lisses choisi parmi l'aminophylline, le niacinate de xanthinol, et la glucophylline ; un polypeptide choisi parmi la gastrine, la somatostatine, l'insuline, et l'acétate de cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe) ; un agent anti-inflammatoire choisi entre l'indométhacine et le sulindac ; un diurétique choisi parmi l'hydrochlorothiazohydrure, l'amiloride et le chlorothiazohydrure et un agent au choline-ester d'augmentation de l'absorption de formule :

$$[(CH_3)_3N^+CH_2CH_2OR]X^-$$

dans laquelle R est un groupe acyle saturé en C_2 à C_{20}, un groupe acyle en C_2 à C_{20}, avec de 1 à 6 double liaisons, un groupe hydroxyacyle en C_2 à C_{20}, avec de 1 à 3 groupements hydroxy, un groupe cétoacyle en C_4 à C_{20}, un groupe hydroxyacyle insaturé en C_5 à C_{20}, un groupe carbalkoxyacyle en C_5 à C_{20} ou un groupe carboxyacyle en C_4 à C_{20} et X est un contre-ion pharmaceutiquement acceptable.

2. Une composition pharmaceutique selon la revendication 1, caractérisée en ce que ledit agent d'augmentation de l'absorption est choisi entre l'hexanoylcholine, l'octanoylcholine, la décanoylcholine, la lauroylcholine, la myristoylcholine, la palmitoylcholine, la stéaroylcholine, la 2-hexènoylcholine, la 9-décènoylcholine, la 9-hexadécènoylcholine, l'α-linoléoylcholine, la 2-hydroxylauroylcholine, la 2-hydroxymyristoylcholine, la 6-cétodécanoylcholine, la 12-hydroxy-12-octadécènoylcholine, l'ω-éthoxycarbonyloctanoylcholine et la 2-hydroxypalmitoylcholine.

3. La composition de la revendication 2 dans laquelle ledit antibiotique β-lactamine est la céfoxitine, ledit aminoglycoside est la gentamycine, ledit agent antiviral est la cytarabine, ledit acide aminé est la méthyldopa, ledit polypeptide est l'acétate de cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe), ledit agent antiinflammatoire est l'indométhacine et ledit diurétique est l'hydrochlorothiazohydrure et ledit agent d'augmentation de l'absorption est la palmitoylcholine, la lauroylcholine, la myristoylcholine ou son sel.

4. La composition de la revendication 3, dans laquelle ledit agent d'augmentation de l'absorption est le chlorure de lauroylcholine.

5. La composition de la revendication 3, dans laquelle ledit agent d'absorption est l'iodure de palmitoylcholine.

6. La composition de la revendication 1, comprenant de plus des excipients pharmaceutiquement acceptables.

Patentansprüche

1. Pharmazeutische Zusammensetzung zur Förderung der Absorption eines oral oder rectal verabreichten Medikaments im Magen-Darm-Trakt, welche eine therapeutisch wirksame Dosismenge eines Medikaments, das ein aus Cefoxitin, Ampicillin, Cefamandol, Cefazolin, Cefotaxim, Cefaclor, Cephalexin, Ceftriaxon, Ceftizoxim, Sarmoxacillin, N-Formamidinyl-thienamycin, Cefadroxil, Penicillin G und Penicillin v ausgewähltes β-Lactam-Antibiotikum, ein aus Gentamycin, Neomycin, Clindamycin, Astromycin, Betamycin und Josamycin ausgewähltes Aminoglycosid, ein aus Cytarabin, Acyclovir, Trifluridin und Vidarabin ausgewähltes Antivirusmittel, eine aus Methyldopa, Levodopa und Carbidopa ausgewählte Aminosäure, ein aus Aminophyllin, Zanthinolniacinat und Glucophyllin ausgewähltes Relaxous für die glatte Muskulatur, ein aus Gastrin, Somatostatin, Insulin und Cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe)-acetat ausgewähltes Polypeptid, ein aus Indomethacin und Sulindac ausgewähltes entzündungshemmendes Mittel, ein aus Hydrochlorthiazid, Amilorid und Chlorthiazid ausgewähltes Diuretikum sowie einen Cholinester als absorptionsförderndes Mittel der Formel umfaßt

$$[(CH_3)_3N^+CH_2CH_2OR]X^-$$

worin R gesättiges Acyl (C_2-C_{20}), Acyl (C_2-C_{20}) mit 1 bis 6 Doppelbindungen, Hydroxyacyl (C_2-C_{20}) mit 1 bis 3 Hydroxygruppen, Ketoacyl (C_4-C_{20}), ungesättigtes Hydroxyacyl (C_5-C_{20}), Carbalkoxyacyl (C_5-C_{20}) oder Carboxyacyl (C_4-C_{20}) ist und X ein pharmazeutisch annehmbares Gegenion ist.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß das die Absorption fördernde Mittel aus Hexanoylcholin, Octanoylcholin, Decanoylcholin, Lauroylcholin, Myristoylcholin, Palmitoylcholin, Stearoylcholin, 2-Hexenoylcholin, 9-Decenoylcholin, 9-Hexadecenoylcholin, α-Linoleoylcholin, 2-Hydroxyylauroylcholin, 2-Hydroxymyristoylcholin, 6-Ketodecanoylcholin, 12-Hydroxy-12-octadecenoylcholin, ω-Ethoxycarbonyloctanoylcholin und 2-Hydroxypalmitoylcholin ausgewählt ist.

3. Zusammensetzung nach Anspruch 2, worin das β-Lactam-Antibiotikum Cefoxitin ist, das Aminoglycosid Gentamycin ist, das Antivirusmittel Cytarabin ist, die Aminosäure Methyldopa ist, das Polypeptid Cyclo-(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe)acetat ist, das entzündungshemmende Mittel Indomethacin ist und das Diuretikum Hydrochlorthiazid ist und das absorptionsfördernde Mittel Palmitoylcholin, Lauroylcholin, Myristoylcholin, Stearoylcholin oder ein Salz davon ist.

4. Zusammensetzung nach Anspruch 3, worin das absorptionsfördernde Mittel Lauroylcholinchlorid ist.

5. Zusammensetzung nach Anspruch 3, worin das absorptionsfördernde Mittel Palmitoylcholiniodid ist.

6. Zusammensetzung nach Anspruch 1, welche weiterhin pharmazeutisch annehmbare Excipienten umfaßt.